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Plasma renin activity and Covid-19 infection: Friends or foe?

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Abstract
Controversies have emerged regarding the effect of Renin-angiotensin-system (RAS) inhibitors on ACE2 regulation and SARS-CoV-2 infection progression in this pandemic. Several countries including India are reporting SARS-CoV-2 infection in huge numbers of asymptomatic carriers. I propose that plasma renin activity (PRA) level may act as a significant pathophysiologic marker to determine the fate of SARS-CoV-2 infection.

Keywords: covid-19, plasma renin activity (PRA), angiotensin, kidney, ace2

Introduction

An ongoing global epidemic of novel coronavirus (SARS-CoV-2), was first reported from Wuhan, China [1]. As of April 15, 2020, it has spread globally to over 210 countries [2]. with 8,708,008 confirmed cases and 461,715 deaths [3]. Since the first detection in January 30, 2020, SARS-CoV-2 cases in India has increased substantially with 410,461 confirmed cases and 13,254 deaths till June 21, 2020 [3]. Several organs of the human body are reported to be affected by the virus with different degrees of severity; *viz*. lungs, heart, kidneys etc. Most important the virus affects the respiratory system with severe effects on the lungs, leading to fatal pathology-driven consequences.

Covid-19 and the Kidney

Besides lungs, a recent report suggest that human kidney is targeted by SARS-CoV-2 infection as the virus was found in kidney tubules of autopsy samples [4]. A retrospective cohort study of 191 patients showed that Covid-19 patients with hypotension are highly susceptible to acute kidney injury (AKI) [5]. The third study with 710 patients showed high prevalence of kidney impairment (haematuria, proteinuria and kidney dysfunction) in hospitalized COVID-19 patients [6]. Another study, based on single-cell transcriptome analysis, demonstrated that the virus-induced cytopathic effect and systemic inflammatory response leads to AKI during Covid-19 outbreak, ensuring risk for severe outcomes and mortality [7]. Thus, the kidney may play a crucial role in host pathogenesis in Covid-19 infection.

The renin–angiotensin system (RAS) is the waterfall of vasoactive peptides that organize several key processes in the human body. Previous reports have suggested the role of angiotensin convertase enzyme-2 (ACE2) in severe acute respiratory syndrome coronavirus (SARS-CoV) induced lung injury [8]. Both SARS-CoV and SARS-CoV-2 bind to ACE2, expressed on their target cells in lungs, kidney, intestine and blood vessels. This binding has been proposed to be the most potential factor for infectivity and/or susceptibility to the disease, being a vital virulence factor in this COVID-19 pandemic.

Recently, controversies have emerged regarding the effect of Renin-angiotensin-system (RAS) inhibitors on ACE2 regulation and SARS-CoV-2 infection progression. We think that RAS maybe influencing SARS-CoV-2 by some other indirect mechanism of control from other organ/s.

Covid-19 and Renin

Renin is released into the circulation by the kidneys and rate limits angiotensin II (Ang II) productions to regulate cardiovascular, pulmonary and renal function via RAS. Plasma renin activity (PRA) is primarily regulated by differential handling of renal sodium-potassium ions. A study has identified prevailing hypokalaemia in COVID-19 patients [9].

We hypothesize that low plasma renin activity (PRA) decreases the risk of lung invasion by SARS-CoV-2. Low PRA could lead to low conversion of angiotensinogen into angiotensin I (Ang-I) and the latter to angiotensin II (Ang-II). Diminished production of Ang-II enhances generation of Ang-[1-7] and Mas receptor (MasR) activation. MasR upregulation promotes vasodilation, anti-oxidant production for attenuation of inflammation, lung injury and fibrosis. The protective effect of Ang- [1-7] can also be initiated by neutral endopeptidase (NEP) or neprilysin (CD10). NEP inactivates natriuretic peptides that promotes diuresis, natriuresis and vasodilation. Those with hypertension and low PRA respond well with natriuretic drugs (anti-V drug types). Furthermore, low levels of Ang-I and Ang-II would directly down-modulate ACE2 expression and may lead to protection against respiratory viruses, like SARS-CoV-2. On the other hand, the absence of abundant PRA would lead to blockade of the harmful AT1 receptor (AT1R) mediated signalling, that promotes inflammation, vasoconstriction, lung fibrosis and acute lung injury. In addition, low PRA may also lead to physiological accumulation of Bradykinin for local release of histamine for initiation of dry incessant cough. According to this speculation, the kidney indirectly controls lung pathology through low PRA for controlling RAS, which requires further validation.

Another interesting aspect is that plasma vitamin D3 levels has negatively affected PRA [10]. Importantly, deficiency of vitamin D increases the risk of respiratory tract infections and tuberculosis. Studies can be designed to investigate this association in individuals with low PRA by vitamin D supplementation for treatment and prophylaxis of SARS-CoV-2 infections. Currently, Africa has fewer cases of

COVID-19 compared to most other parts of the world. There are several speculations attributing the reason of low spread; low level of urbanization, warmer temperatures, lack of testing etc. Low PRA was found in the population of African origin [11], we speculate that this could be responsible for low incidence of SARS-CoV-2. Several studies have shown that low renin levels are prevalent in blacks compared to whites; leading to diminished β2-adrenoreceptor activity, increased response to Ang-II inhibition and increased intracellular calcium in kidney. Additionally, polymorphic variants have been identified in the *Renin* gene which may differentially regulate PRA and blood pressure [12]. *Renin* gene polymorphism was associated with hypertension in a Chinese population [13]. Several countries are also reporting SARS-CoV-2 infection in asymptomatic carriers. Prospective cohort studies can be initiated to investigate the role of PRA and *Renin* gene variants in asymptomatic and symptomatic presentations of SARS-CoV-2 infection.

Conclusion

A recent study on autopsy samples of COVID-19 patients has confirmed that SARS-CoV-2 infection, in addition to the lungs, damages vessels, kidney and other organs (14). The existing epidemiological data have confirmed that diabetes is the main renal comorbidity and AKI is one of the main risk factors in the prognosis of COVID-19. However, the potential impact of this infection on patients affected by end-stage renal disease and/or transplantation is still not comprehensible at this phase of the current pandemic. Importantly, this pandemic poses huge challenges for patients on dialysis. Notably, PRA may be altered by antihypertensive agents (*viz*., ACE inhibitors, beta-blockers, and diuretics), renin-inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs). We propose the PRA level as a probable significant pathophysiologic marker to determine the fate of SARS-CoV-2 infection. Before drawing conclusions, the role of PRA needs to be studied by rapid initiation of clinical trials, prospective hospital and community level evidence-based studies.

Conflict of interest

None reported

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None

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